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WO 03/014082 A1

(54) Title: CYCLOPENTA ' B ! INDOLE DERIVATIVES AS SPLA2 INHIBITORS

(57) **Abstract:** A novel class of tricyclic compounds of the following formula (I) is disclosed together with the use of such compounds for inhibiting $sPLA_2$ mediated release of fatty acids for treatment of Inflammatory Diseases such as septic shock.

CYCLOPENTA ' B I INDOLE DERIVATIVES AS SPLA2 INHIBITORS.

Field of the Invention

This invention relates to novel tricyclic compounds useful for Inflammatory Diseases.

Background of the Invention

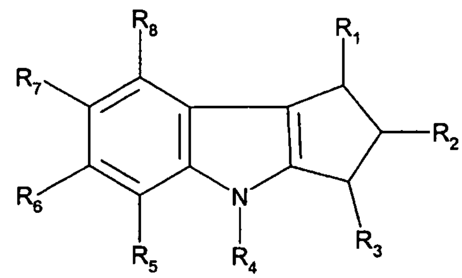
The structure and physical properties of human non-pancreatic secretory phospholipase A_2 (hereinafter called, "$sPLA_2$") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A_2 Present in Rheumatoid Arthritic Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.; Kloss, Jean; and Johnson, Lorin K.; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335-5338, 1989; and "Structure and Properties of a Human Non-pancreatic Phospholipase A_2" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky, R. Blake; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5768-5775, 1989; the disclosures of which are incorporated herein by reference.

It is believed that $sPLA_2$ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds, which inhibit $sPLA_2$ mediated release of fatty acids (e.g., arachidonic acid). Such compounds would be of value in the general treatment of conditions induced and/or maintained by overproduction of $sPLA_2$; such as sepsis or pain. There is a dearth of effective treatment for diseases associated with $sPLA_2$ mediated release of fatty acids, particularly sepsis.

Therefore, it is desirable to develop new compounds and treatments for $sPLA_2$ induced diseases.

Summary of the Invention

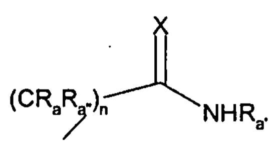
The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or enantiomers thereof, useful for the treatment or prevention of Inflammatory Diseases:



(I)

wherein;

R_1 is an amide, thioamide or hydrazone group represented by the formulae,



wherein X is oxygen or sulfur; R_a and $R_{a'}$ are independently selected from hydrogen, $(C_1\text{-}C_8)$alkyl, or aryl; $R_{a''}$ is hydrogen, NH_2, $(C_1\text{-}C_8)$alkyl, aryl, $(C_1\text{-}C_8)$alkylaryl, or arylalkyl; and n is 0, 1, or 2.

R_2, and R_3 are independently hydrogen, or a group containing 1 to 10 non-hydrogen atoms plus any required hydrogen atoms;

R_4 is the group (C_1-C_{20})alkyl, (C_1-C_{20})haloalkyl, (C_2-C_{20})alkenyl, (C_2-C_{20})alkynyl, (C_1-C_{10})alkylaryl, (C_1-C_5)alkylcyclohexyl, (C_1-C_5)alkylcyclopentyl, (C_1-C_5)alkylcycloheptyl, phenyl, benzyl, methylnaphthyl, (C_1-C_5)alkylheterocyclic, carbocyclic radical, or heterocyclic radical, or aryl;

R_5, R_6, and R_7 are independently selected from hydrogen and non-interfering substituents;

R8 is the group, -(La)-(acidic group) wherein $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

The present invention provides novel tricyclic compounds of formula I having potent and selective effectiveness as inhibitors of mammalian $sPLA_2$.

The present invention also relates to the use of novel tricyclic compounds of formula I useful in the treatment and/or prevention of Inflammatory Diseases.

The present invention also relates to the use of a novel tricyclic compound of formula I to inhibit mammalian $sPLA_2$ mediated release of fatty acids.

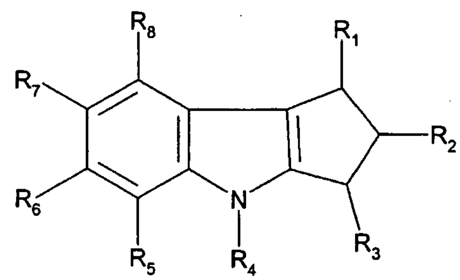
The present invention provides a pharmaceutical composition containing any one of the tricyclic compounds of the invention.

The present invention also relates to the use of a formulation comprising a compound of formula I, and a carrier or diluent for the treatment or prevention of sepsis

The present invention relates to the use of a pharmaceutical composition comprising a therapeutically effective amount of $sPLA_2$ inhibitor compounds of formula I and mixtures thereof for the manufacture of a medicament for the treatment of Inflammatory Diseases.

The present invention relates to a of a pharmaceutical composition comprising a therapeutically effective amount of $sPLA_2$ inhibitor compounds according to Claim 1 and mixtures thereof for the manufacture of a medicament for the treatment of Inflammatory Diseases.

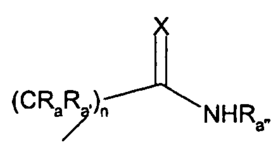
The present invention relates to the use of a compound of formula I for the manufacture of a medicament for the treatment or prevention of Inflammatory Diseases comprising administering a therapeutically effective amount of a tricyclic compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(I)

wherein;

R_1 is an amide, thioamide or hydrazone group represented by the formulae,



wherein X is oxygen or sulfur; R_a and $R_{a'}$ are independently selected from hydrogen, $(C_1\text{-}C_8)$alkyl, or aryl; $R_{a''}$ is hydrogen, NH_2, $(C_1\text{-}C_8)$alkyl, aryl, $(C_1\text{-}C_8)$alkylaryl, or arylalkyl; and n is 0, 1, or 2.

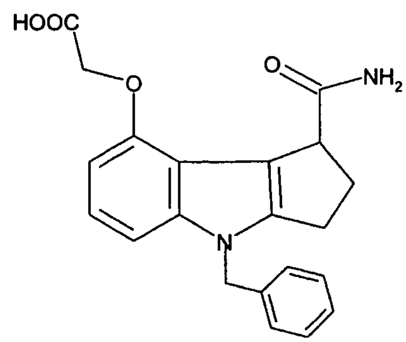
R_2, and R_3 are independently hydrogen, or a group containing 1 to 10 non-hydrogen atoms plus any required hydrogen atoms;

R_4 is the group (C_1-C_{20})alkyl, (C_1-C_{20})haloalkyl, (C_2-C_{20})alkenyl, (C_2-C_{20})alkynyl, (C_1-C_{10})alkylaryl, (C_1-C_5)alkylcyclohexyl, (C_1-C_5)alkylcyclopentyl, (C_1-C_5)alkylcycloheptyl, phenyl, benzyl, methylnaphthyl, (C_1-C_5)alkylheterocyclic, carbocyclic radical, or heterocyclic radical, or aryl;

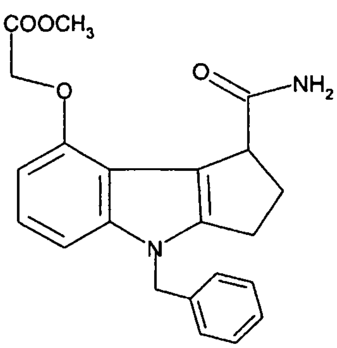
R_5, R_6, and R_7 are independently selected from hydrogen and non-interfering substituents;

R8 is the group, -(La)-(acidic group) wherein $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

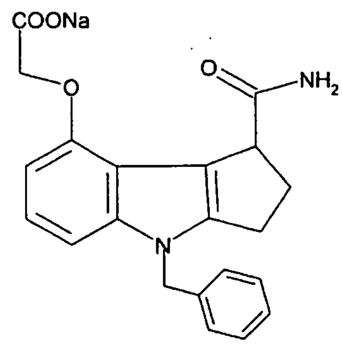
The present invention relates to the use of a compound of formula I for the manufacture of a medicament for the treatment or prevention of Inflammatory Diseases comprising administering a therapeutically effective amount of a tricyclic compound represented by the formulae (C1), (C2), or (C3):



C1



C2



C3

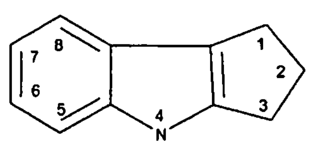
I. Definitions:

The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, asthma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathric spondylitis, prostrate cancer, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris,

pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of the compound of formula I in an amount sufficient to inhibit $sPLA_2$ mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.

The term, "tricyclic", or "tricyclic nucleus" as used herein refers to a nucleus (having numbered positions) with the structural formula (X):



(X)

The tricyclic compounds of the invention employ certain defining terms as follows:

The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as

methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, sec-butyl, n-pentyl, and n-hexyl.

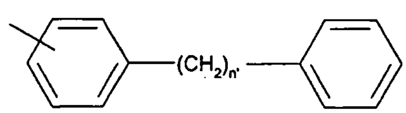
The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated number ranges of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodinyl, piperidinyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, benzo(b)thiophenyl, carbazolyl, norharmanyl, azabenzo(b)thiophenyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1.2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridylyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl, morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidinyl, hexamethyleneiminium, heptamethyleneiminium, piperazinyl and quinoxalinyl.

The term "(C_1-C_5)alkylcyclopentyl," "(C_1-C_5)alkylcyclohexyl," or "(C_1-C_5)alkylheterocyclic" represent a (C_1-C_5)alkyl group attached respectively to a cylopentyl, cyclohexyl, and heterocyclic group wherein the entire group is attached to the tricyclic nucleus (X) at the alkyl terminus. Therefore the mass of the entire group is the mass of the (C_1-C_5)alkyl group plus the cyclopentyl, cyclohexyl or heterocyclic group to which it is attached.

The term, "carbocyclic radical" refers to radicals derived from a saturated or unsaturated, substituted or unsubstituted 5 to 14 membered organic nucleus whose ring forming atoms (other than hydrogen) are solely carbon atoms. Typical carbocyclic radicals are cycloalkyl, cycloalkenyl, phenyl, benzyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, toluyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, and anthracenyl, biphenyl, dibenzylyl and related dibenzylyl homologues represented by the formula (a):



(a)

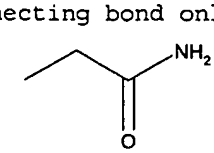
where n' is a number from 1 to 8.

The terms, "non-interfering substituent", or "non-interfering groups" refer to radicals suitable for substitution at positions 2, 3, 5, 6, and/or 7 of the tricyclic nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_7-C_{12})arylalkyl, (C_7-C_{12})alkylaryl, $(C_3-$

C_8)cycloalkyl, (C_3-C_8)cycloalkenyl, phenyl, benzyl, toluyl, xylenyl, biphenyl, (C_1-C_8)alkoxy, C_2-C_8)alkenyloxy, C_2-C_8 alkynyloxy, (C_2-C_{12}) alkoxyalkyl, (C_2-C_{12})alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, (C_2-C_{12})alkylcarbonylamino, (C_2-C_{12})alkoxyamino, (C_2-C_{12})alkoxyaminocarbonyl, (C_1-C_{12})alkylamino, (C_1-C_6)alkylthio, (C_2-C_{12})alkylthiocarbonyl, (C_1-C_8)alkylsulfinyl, (C_1-C_8)alkylsulfonyl, (C_2-C_8)haloalkoxy, (C_2-C_8)haloalkylsulfonyl, (C_2-C_8)haloalkyl, (C_2-C_8)hydroxyalkyl, -C(O)O((C_2-C_8)alkyl), -$(CH_2)_n$-O-(C_1-C_8 alkyl), benzyloxy, phenoxy, phenylthio, -($CONHSO_2R$), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8; and R is (C_1-C_8)alkyl.

The term "substituted group" is an organic group substituted with one or more non-interfering substituents.

As used herein the terms "group", "radical" or "fragment" are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments of molecules. For example acetamide group represent the acetamide fragment or radical. Structures of groups, radicals or fragments attached to the tricyclic nucleus have been drawn to show the first line as a connecting bond only. Thus, the group

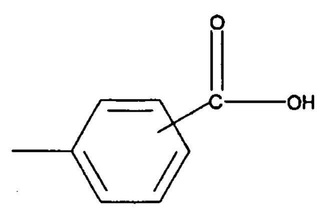


represents the acetamide radical or group, not the propanamide radical unless otherwise indicated.

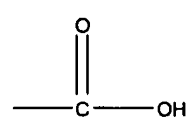
The term, "(acidic group)" means an organic group which when attached to a tricyclic nucleus at the 8-position, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

-5-tetrazolyl,

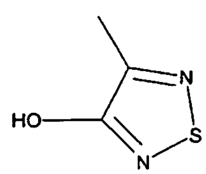
$-SO_3H$,



,



or



The term, "amine", includes primary, secondary and tertiary amines.

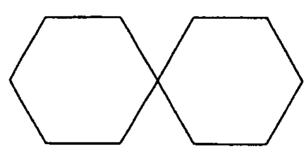
The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals, $-CH_2-CH_2-$ and $-CH_2-$.

The term, "acid linker length" refers to the number of groups or atoms directly connecting from the tricyclic

nucleus to the acidic group. For example, the group $-OCH_2-$ has an acid linking length of 2.

The term, "group containing 1 to 10 non-hydrogen atoms" refers to relatively small groups which form substituents at the designated position of the tricyclic nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as $-CF_3$, -Cl, -Br, $-NO_2$, -CN, $-SO_3$; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as $-CH_3$, $-C_2H_5$, and $-CH=CH_2$.

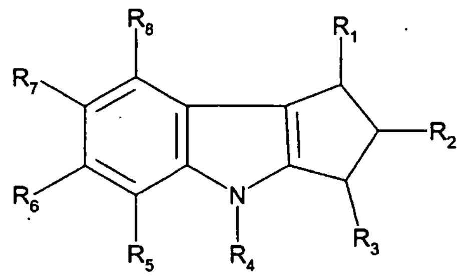
The term "spiro[5.5]undecanyl" refers to the group represented by the formula;



II. The tricyclic Compounds of the Invention:

The present invention provides a novel class of tricyclic compounds useful as $sPLA_2$ inhibitors for the treatment and/or prophylaxis of inflammation attendant to Inflammatory Diseases

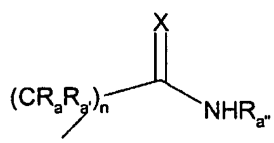
The compounds of the invention are represented by the general formula (I) and include pharmaceutically acceptable salts, racemates, enantiomers, or solvates thereof;



(I)

wherein;

R_1 is an amide, thioamide or hydrazone group represented by the formulae,



wherein X is oxygen or sulfur; R_a and $R_{a'}$ are independently selected from hydrogen, $(C_1\text{-}C_8)$alkyl, or aryl; $R_{a''}$ is hydrogen, NH_2, $(C_1\text{-}C_8)$alkyl, aryl, $(C_1\text{-}C_8)$alkylaryl, or arylalkyl; and n is 0, 1, or 2.

R_2, and R_3 are independently hydrogen, or a group containing 1 to 10 non-hydrogen atoms plus any required hydrogen atoms;

R_4 is the group $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{20})$haloalkyl, $(C_2\text{-}C_{20})$alkenyl, $(C_2\text{-}C_{20})$alkynyl, $(C_1\text{-}C_{10})$alkylaryl, $(C_1\text{-}C_5)$alkylcyclohexyl, $(C_1\text{-}C_5)$alkylcyclopentyl, $(C_1\text{-}C_5)$alkylcycloheptyl, phenyl, benzyl, methylnaphthyl, $(C_1\text{-}C_5)$alkylheterocyclic, carbocyclic radical, or heterocyclic radical, or aryl;

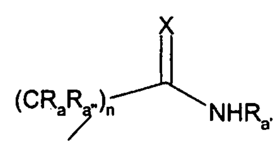
R_5, R_6, and R_7 are independently selected from hydrogen and non-interfering substituents;

R8 is the group, -(La)-(acidic group) wherein -(L_a)-, is an acid linker having an acid linker length of 1 to 8;

Preferred Subgroups of Compounds of Formula (I):

Preferred R_1 substituents:

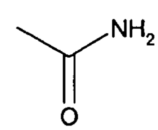
A preferred subgroup of R_1 is an amide, thioamide or hydrazone group represented by the formula,



wherein X is oxygen or sulfur; R_a and $R_{a'}$ are independently selected from hydrogen, $(C_1\text{-}C_8)$alkyl, or aryl; $R_{a''}$ is hydrogen, NH_2, $(C_1\text{-}C_8)$alkyl, aryl, $(C_1\text{-}C_8)$alkylaryl, or arylalkyl; and n is 0, 1, or 2.

A more preferred subclass of compounds of formula (I) are those wherein X is oxygen.

Also more preferred is a subclass of compounds of formula I wherein R_1 is an amide group represented by



Preferred R_2 substituents:

R_2 is preferably selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, -O-($(C_1\text{-}C_4)$alkyl), -S-($(C_1\text{-}C_3)$alkyl), -$(C_3\text{-}C_{10})$cycloalkyl, $-CF_3$, halo, $-NO_2$, -CN, $-SO_3$. Particularly preferred R_7 groups

are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, $-CF_3$, -Cl, -Br, or $-O-CH_3$.

Preferred R_3 substituents:

R_3 is preferably selected from the group consisting of hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, $-O-((C_1-C_4)$alkyl), $-S-((C_1-C_3)$alkyl), $-(C_3-C_{10})$cycloalkyl, $-CF_3$, halo, $-NO_2$, -CN, $-SO_3$. Particularly preferred R_6 groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, $-CF_3$, -Cl, -Br, or $-O-CH_3$.

Preferred R_4 substituents:

Preferred R_4 groups are selected from the group consisting of (C_1-C_{20})alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_{10})alkylaryl, cyclohexylmethyl, cyclopentylmethyl, ethylcyclohexyl, ethylcyclopentyl, methylcycloheptyl, phenyl, benzyl, methylnaphthyl,and aryl radicals.

Preferred R_5, R_6, and R_7 Groups

A preferred R_5 or R_6 or R_7 group is a group independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, $-OCH_3$, $-OCH_2CH_3$, halogen, phenyl and phenoxy.

Preferred R_8 substituents:

A preferred subgroup of R8 is the group -(La)-(acidic group) wherein $-(L_a)-$, is an acid linker having an acid linker length of 1, 2 or 3 atoms;

Also preferred is a subclass of compounds of formula I wherein $-(L_a)-$ is an acid linker selected from the group consisting of;

$$\left[\!-\!O\!-\!CH_2\!-\!\right] ,$$

$$\left[\!-\!S\!-\!CH_2\!-\!\right] ,$$

$$\left[\!-\!\overset{H}{N}\!-\!CH_2\!-\!\right] ,$$

$$\left[\!-\!\underset{H_2}{C}\!-\!\underset{H_2}{C}\!-\!\right] ,$$

A most preferred subgroup of R8 is the group, -(La)-(acidic group) wherein $-(L_a)-$, is an acid linker represented by $\left[O-CH_2\right]$.

A preferred compound of the invention is a compound selected from the group consisting of:

(4-benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(2-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(2-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cyclopropylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cyclobutylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cyclopentylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cycloheptylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(4-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(3-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(1-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,3-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,3-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,6-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(2-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(2-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(4-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

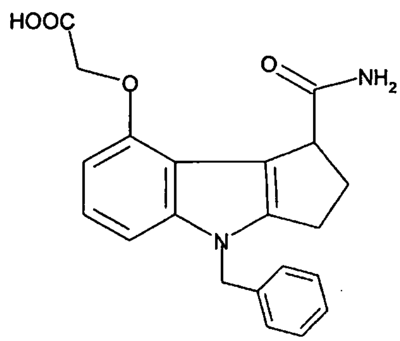
(4-[(3-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cyclopropylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cyclobutylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cyclopentylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cycloheptylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(4-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

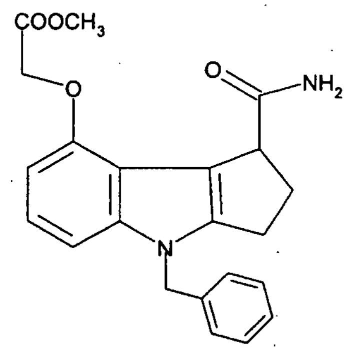
(4-[(1-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,3-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
2,3-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,6-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(3,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(phenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, morpholinoethyl ester,
(4-[(cyclohexyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, morpholinoethyl ester,
(4-[(cyclopentyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, morpholinoethyl ester,
(4-[(phenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, N,N-diethylacetamido ester,
(4-[(cyclohexyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, N,N-diethylacetamido ester, and
(4-[(cyclopentyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, N,N-diethylacetamido ester.

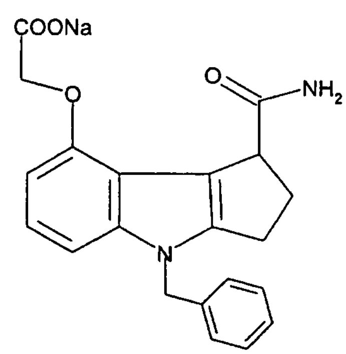
Preferred compounds of the invention are represented by the formulae (C1), (C2), or (C3):



C1



C2



C3.

The salts of the tricyclic compounds represented by formula (I), are an additional aspect of the invention.

In those instances when the compound of the invention possesses acidic or basic functional groups, various salts may be formed which are more water soluble and more physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, hydrobromide, camsylate, carbonate, chloride, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrochloride, hydroxynaphthoate, hydroiodide, isothionate, lactate, lactobionate, laurate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate,

stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers, and thus, may exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group, there exist the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereo-specific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of stereoisomers and diastereomers, because they have different melting points, different boiling points, and different solubilities and can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid

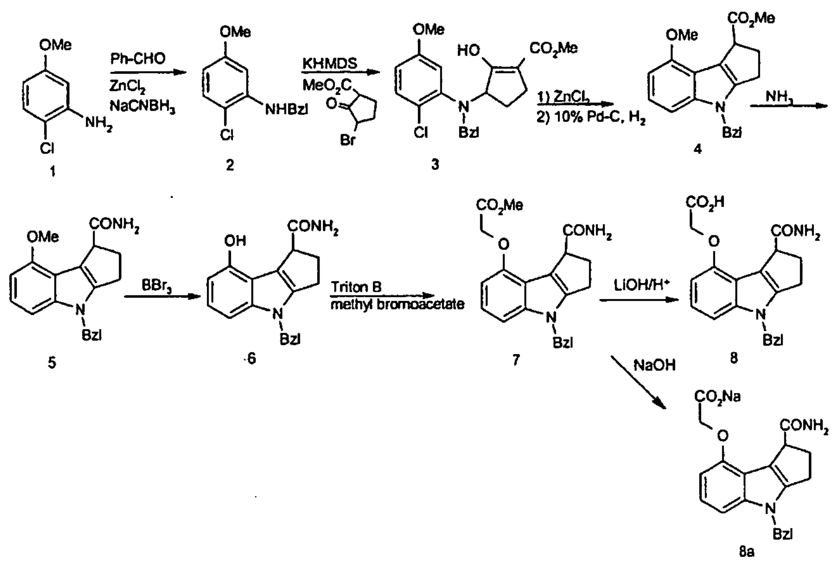
and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6). Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of formula (I) (in a medium such as dimethylformamide) with 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4, 220-3).

(III) Method of preparing the tricyclic compound:

The tricyclic compounds of the present invention are prepared by following a scheme such as Scheme 1 shown below:

Scheme 1



Scheme 1 depicts a protocol for preparing tricyclic-compounds of the invention starting from 6-chloro-m-anisidine (1) (available from Aldrich Chemical Co. Milwaukee U.S.A, and other fine chemical suppliers) or substituted analogs thereof. As shown, the starting material (1) is reductively aminated with benzaldehyde using a mixture of zinc chloride and sodium cyanoborohydride as reducing agents to form the compound (2). One of skill in the art is aware that the reaction to prepare (2) may be accomplished with other reducing agents including but not limited to $NaBH_4$, HCl/Zn, and $NaCNBH_3$. The choice of aldehyde or ketone to be

reductively aminated with compound (1) determines the structure of the group R_4. For example, the use of formaldehyde in the reductive amination steps would form the N-methyl analog of (2) and ultimately a compound of formula I wherein R_4 is methyl. Similarly, the use of cyclohexylacetaldehyde in the reductive amination steps would form the cyclohexylmethyl analog of (2) and ultimately a compound of formula I wherein R_4 is cyclohexylmethyl. A solution of compound (2) is deprotonated at the nitrogen using a base to form a nucleophile to which is added 2-carbomethoxy-5-bromocyclopentanone. When substitution is desired at positions 2 and/or 3, an appropriately substituted analog of 2-carbomethoxy-5-bromocyclopentanone is employed. The reaction of (2) with 2-carbomethoxy-5-bromocyclopentanone results in a tertiary amine substitution product (compound 3). 2-carbomethoxy-5-bromocyclopentanone and analogs thereof may be prepared by a method similar to that reported by Marx et al. *J. Org. Chem.* ***1972***, *37, 4489*. Strong bases are preferred for de-protonating the nitrogen atom of compound 2. Most preferred is a base selected from potassium(bistrimethylsilyl)amide, lithium diisopropyl amide, and *n*-butyllithium. After the initial base addition at about -60 to -10°C, the reaction is preferably performed at ambient temperatures for about 4 to 24 hours. The product (3) is isolated by aqueous work-up and extraction from organic solvents such as, for example, ethyl acetate. The product (3) may be used directly or further purified by chromatography and/or crystallization by methods known to one of skill in the art. To prepare compound (4), compound (3) dissolved in toluene or other suitable solvent is heated with zinc chloride at reflux temperature over a period of 10 to 60

hours, preferably about 48 hours, to afford an intermediate tricyclic compound. The intermediate compound is reduced by hydrogenation using palladium-on-carbon as catalyst. Preferably, the hydrogenation is performed in ethanol or other protic solvent with triethylamine as acid scavenger. While other reducing catalysts may be used, 10% palladium-on-carbon is preferred. The catalyst is also preferably wetted with ethanol before use.

The methyl ester at the 1-position of compound (4) is converted to the amide by reaction of compound (4) with excess ammonia solution. Other methods for the conversion of esters to amides are known to one of skill in the art and may be found in general reference texts (see J. March, Advanced Organic Chemistry, 3rd ed., Wiley Interscience Publishers, New York, NY, 1985).

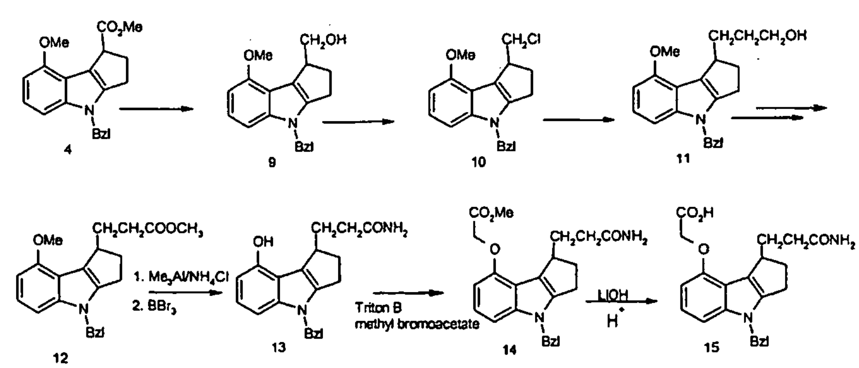
The compound (5) is de-methylated by reaction with boron tribromide or sodium thioethoxide in a suitable solvent such as dichloromethane. About 1.0 to 12.0 equivalents of boron tribromide is typically sufficient to effect complete de-methylation. The de-methylation reaction temperature is from about -12°C to about 10°C. Work-up is initiated by stirring with methyl alcohol or other suitable protic solvent. The stirring in methyl alcohol is followed by neutralization with a base such as sodium bicarbonate. This is followed by extraction and purification of the organic phase by methods known to one of skill in the art. The product (6) is then dissolved in N,N-dimethylformamide followed by addition of a slight excess (about 1.05 mole equiv. based on (5)) of TRITON-B™ (Aldrich Chemical Company, Milwaukie, USA), cesium carbonate or other mild base, and methyl bromoacetate. The mixture is stirred at ambient temperature to afford compound (7) after about 1 to 6 hours of reaction.

Compound (7) is isolated by aqueous wash followed by chromatography of the organic layer. Other 2-substituted haloacetates i.e. benzyl bromoacetate may be used to prepare, for example, the benzyl analog of (7).

The free acid (8) is obtained by acidifying the saponification product of (7) or other basification reaction product, e.g. with potassium or lithium hydroxide. Most strong inorganic acids are suitable for acidification as described previously. However, the use of dilute HCl is preferred. The free acid (8) may be extracted into an organic phase if soluble, and dried by common laboratory methods or dried by removing water from the aqueous phase. Alternatively the saponification reaction (sodium hydroxide reaction with (8a)) product, itself a compound of the invention, may be isolated.

Preparation of homologous amide derivatives of (I) may be accomplished by methods known to one of skill in the art as shown for example for the propanamide derivative below in Scheme 2.

Scheme 2



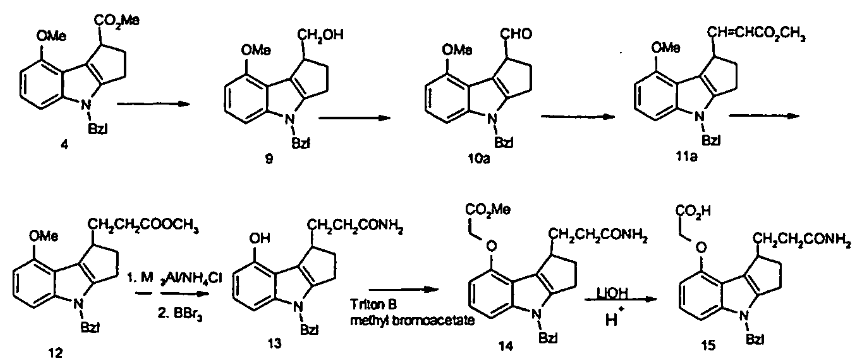
Compound (4) from Scheme 1 is reduced to the alcohol (9), for example by lithium hydride reductions or by other methods known to one of skill in the art. The resulting alcohol (9) may be converted to the halide, preferably chloride (10). The halogenation of the alcohol (9) may be

accomplished by use of a thionyl halide or other methods known to one of skill in the art. The halide (10) may be activated by halogen-metal exchange reaction using for example, n-butyllithium. The activated product of (10) is then reacted with ethylene oxide, for example, to afford the terminal alcohol compound (11). Conversion of the terminal alcohol (11) to an ester via an intermediate acid may be accomplished, for example, by oxidation of the alcohol (11) with sodium hypochlorite in buffered *t*-butanol followed by esterification of the incipient acid to the ester (12). Methods for these conversions are known to one of skill in the art and may also be found in general reference texts that have been discussed previously.

The ester (12) may be converted to the corresponding amide derivative (13) or other substituted amide compound. For example, the reaction of the ester (12) with methylchloroaluminum amide in benzene or other suitable solvent or solvent mixtures affords an intermediate amide (See Levin, J.I.; Turos, E.; Weinreb, S.M. *An alternative procedure for the aluminum-mediated conversion of esters to amides*. *Syn.Comm.*, 1982, *12*, 989-993). The intermediate amide from (12) is then de-protected at the 8-position by the use of boron tribromide as described previously to afford the amide (13). The amide (13) acetylated by reaction with methylbromo acetate and TRITON-B™ (Aldrich Chemical Company, Milwaukee, USA) to afford compound (14). The conversion of compound (14) to the oxyacetic acid (15), salt or ester derivative is accomplished as described previously for Scheme 1.

In an alternate and preferred procedure, the ester (12) may be prepared in a sequence as shown in Scheme 3 below

Scheme 3

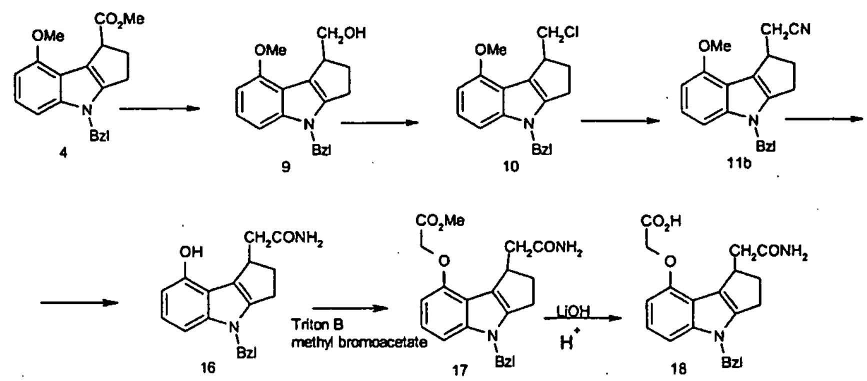


According to Scheme 3, the alcohol (9) may be oxidized to the aldehyde (10a). Oxidation of alcohol (9) to the aldehyde (10a) may be accomplished for example, by the use of sodium hypochlorite in buffered *t*-butanol, or the use of pyridinium sulfur trioxide complex with diisopropyl ethylamine as base in dimethyl sulfoxide solvent (see *Tetrahedron Letters*, 28, 1603 (**1987**)). The aldehyde (10a) is then subjected to a Horner-Emmons modification of the Wittig reaction to afford the α,β-unsaturated ester (11a). Preferably, a reagent for forming the α,β-unsaturated methyl ester (i.e. trimethylphosphonoacetate) is used to react with the aldehyde in the presence of a base. Preferred bases for the Wittig type reactions include n-butyllithium, sodium hydride and sodium ethoxide. The *E* regio-isomer of α,β-unsaturated methyl ester or a preponderance of the E regio-isomer may be obtained. A general review of Wittig and modified Wittig reactions is provided in *Chem. Rev.*, 89 863 (**1989**). However, the regio-isomerism of the modified Wittig reaction is irrelevant because of the subsequent reduction step. The unsaturated ester (11a) is reduced to afford compound (12), preferably by hydrogenation techniques such as use of hydrogen with Palladium-on-carbon catalysts. The saturated ester (12) is then converted to the amide (13) and

ultimately to compound (15) and analogs thereof as shown in Scheme 3, and described previously for Scheme 1.

Compounds of formula (I) wherein for R_1 n is 1, may be prepared by a Scheme such as Scheme 4 below:

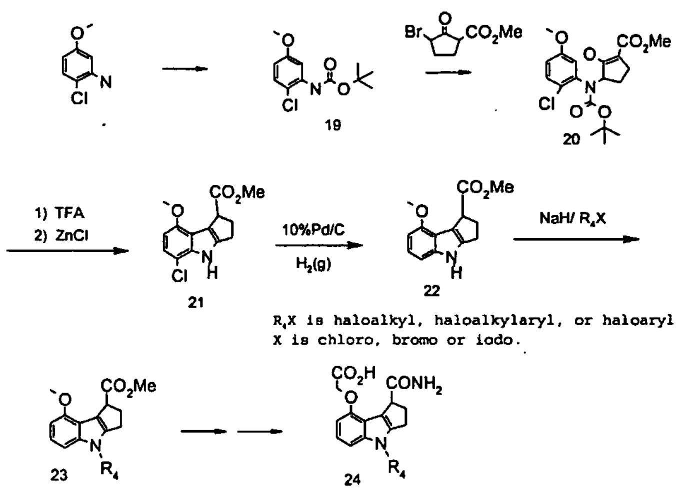
Scheme 4



For example, the halide (10) prepared according to Scheme 2 may be cyanated using sodium cyanide or a soluble source of cyanide ion to afford the cyano compound (11b). The cyano compound (11b) may be hydrolyzed to afford the amide compound (16). The amide (16) is converted to compound (18) or analogs such as the oxyacetic acid methyl ester (17), or oxyacetic acid, sodium salt derivatives as discussed previously. A preferred procedure for the conversion of (11b) to (16) is the use of a hydrogen peroxide/potassium carbonate mixture in dimethyl sulfoxide solvent. The reaction is typically performed at ambient temperatures and the product is worked up by acidic aqueous quench followed by extraction. Other procedures for the conversion of the cyano group to the amide group may be found in previously disclosed general reference texts.

To prepare compound of formula (I) wherein R_4 is a halo-substituted group, i.e. R_4 is halosubstituted benzyl or (C_1-C_{20})haloalkyl wherein the halo group is chloro, bromo, fluoro or iodo, the process as shown in Scheme 5 below may be utilized.

Scheme 5



Scheme 5 in addition to its utility in preparing compounds of formula I also provides the the advantage of allowing alkylation of the tricyclic nitrogen (4- position of tricyclic nucleus) with haloaryl, haloalkylaryl, or haloalkyl groups after formation of the tricycle to avoid dehalogenation of such groups as may obtain following the procedure of Scheme 1. According to Scheme 5, the 6-chloro-m-anisidine is *BOC*-protected using t-butyloxycarbonyl anhydride (BOC anhydride) or other protecting group to form compound (19). Compound (19) is then substituted with 2-carbomethoxy-5-bromocyclopentanone at the nitrogen to form compound (20), using a base as described for Scheme 1. The product (20) is deprotected with trifluoroacetic acid in a suitable solvent to afford an intermediate compound which is then reductively

cyclized using zinc chloride in a suitable solvent e.g. toluene at reflux to form compound (21). Compound (21) is dehalogenated using 10% palladium-on-carbon to afford compound (22) similar to the procedure of Scheme 1. The dehalogenated product (22) is then arylated or alkylated at the tricyclic nitrogen using a suitable base (in the absence, or presence, of a catalyst) and an appropriately halo-substituted arylhalide or alkylhalide. Arylation of amines can be accomplished by a wide variety of known methods and catalysts and are known to one of skill in the art and may be found in general reference texts (see March's Advanced Organic Chemistry, 5th ed., Wiley Interscience Publishers, New York, NY, 2001, page 501-502), for example, according to the general procedures of Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y.; *Tetrahedron Lett* 2000, 41 (4), 481-483; Wolfe, J. P.; Buchwald, S. L.; *J. Org. Chem.* 1996, 61, 1133; Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M.; *Tetrahedron [TETRAB]* 1998, 54 (19), 4811-4818; Smith W. J., Sawyer J. S., *Tetrahedron Lett* 37(3), 299-302 (1996); and related references. The resulting haloaryl or haloalkyl compound (23) is subjected to procedures similar to that shown in Scheme 1 (see compound 4 of Scheme 1) to afford the desired halosubstituted compound (24).

IV. Methods of Using the Compounds of the Invention:

The tricyclic compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) $sPLA_2$, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting $sPLA_2$ mediated release of fatty acids comprises contacting mammalian $sPLA_2$ with a therapeutically effective amount of tricyclic compounds of Formulae (I) as described herein including a salt or a prodrug derivative thereof.

Another aspect of this invention relates to a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress syndrome, pancreatitis, trauma, asthma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, and related diseases which comprises administering to a mammal (including a human) a therapeutically effective dose of a tricyclic compound of the invention.

As previously noted the compounds of this invention are useful for inhibiting $sPLA_2$ mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of $sPLA_2$ initiated fatty acids by the compounds of the invention. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effect will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention per Formula (I) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The

unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the tricyclic compound of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a

formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substance, which may also act as flavoring agents, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc. A preferred tablet formulation for oral administration is one that affords rapid dissolution in the mouth of a patient in need thereof.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile

water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The Active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of Active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The Active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The Active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50mg of Active ingredient per 5mL dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

Assay

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A_2. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A_2 on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

Reagents:

REACTION BUFFER -

$CaCl_2 \cdot 2H_2O$ (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)
(Sigma A-7030, product of Sigma Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

0.05 $NaOAc.3H_2O$, pH 4.5

0.2 NaCl

Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine

TRITON X-100^{TM} prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

A measured volume of racemic diheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar TRITON X-100^{TM} nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mm Triton X-100^{TM} detergent, and 0.12 mm DTMB in a buffered aqueous solution at pH 7.5.

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
3. Add 50 nanograms of $sPLA_2$ (10 microliters) to appropriate wells;
4. Incubate plate at 40 ^{o}C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

Tests were done in triplicate. Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were re-assayed to confirm their activity and, if sufficiently active, IC_{50} values were determined. Typically, the IC_{50} values (see,

Table I, below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC_{50} values. IC_{50} values were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition.

Results

Compound of Example#	IC_{50} (μM) (micromolar)
1	0.046

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

Experimental

All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory NMR and IR spectra. They also had the correct mass spectral values.

Example 1

Part A.

***N*-benzyl-2-chloro-5-methoxyaniline**

A solution of 6-chloro-*m*-anisidine (9.80 g; 62.2 mmol), benzaldehyde (7.60 mL; 74.62 mmol) and $ZnCl_2$ (10.20 g; 74.62

mmol) in 200 mL of MeOH was treated $NaCNBH_3$ (4.70 g; 74.62 mmol) in 0.5 g portions. The reaction was heated to reflux for about 2 hours, allowed to cool and additional $NaCNBH_3$ (1.95 g; 31.03 mmol) added. The mixture was stirred at ambient temperature for 72 hrs, poured into aqueous 1 N NaOH (400 mL), and extracted multiple times with Et_2O (1 L total). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The black solid was purified by MPLC (1.25 % EtOAc in hexanes) to afford the title compound as an oil (8.46 g; 32.89 mmol; 55%). ^1H NMR ($CDCl_3$) δ 7.44-7.27 (m, 5H), 7.20-7.14 (m, 1H), 6.26-6.18 (m, 2H), 4.72 (br s, 1H), 4.38 (d, J=5.6 Hz, 2H), 3.71 (s, 3H); IR ($CHCl_3$) 1604, 1583, 1513, 1466, 1453, 1318, 1173, 1027 cm^{-1}; FDMS 248 (M+1); Anal. calcd for $C_{14}H_{14}NOCl$: C, 67.88; H, 5.70; N, 5.65. Found: C, 68.05; H, 5.64; N, 5.72.

Part B.

A 0 °C solution of *N*-benzyl-2-chloro-5-methoxyaniline (3.00 g; 12.11 mmol) from part A, in 75 mL THF was treated with potassium bis(trimethylsilyl)amide (0.5 M in toluene; 50.0 mL; 25.0 mmol) in a dropwise manner. After stirring 15 min at 0 °C, a solution of 2-carbomethoxy-5-bromocyclopentanone (Marx et al. J. Org. Chem. (1972), 37, 4489: 2.94 g; 13.32 mmol) in 5 mL THF was added dropwise. The reaction was stirred at ambient temperature for 16 hrs and was quenched with brine (200 mL). The two layers were separated and the aqueous phase extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 4.46 g of an oil. Purification by chromatography (5% EtOAc in hexanes) afforded 2.10 g (5.41 mmol; 45%) of 3-[Benzyl-(2-chloro-5-methoxy-phenyl)-amino]-2-hydroxy-cyclopent-1-enecarboxylic acid methyl ester, compound 3, Scheme 1, as an oil. IR ($CHCl_3$) 1757, 1728, 1592, 1480, 1465, 1446, 1241, 1199, 1173

cm^{-1}; FDMS 388 (M+1); Anal. calcd for $C_{21}H_{22}NO_4Cl.0.4\ H_2O$: C, 63.84; H, 5.43; N, 3.94. Found: C, 63.51; H, 5.64; N, 5.72.

Part C.

A mixture of (3-[Benzyl-(2-chloro-5-methoxy-phenyl)-amino]-2-hydroxy-cyclopent-1-enecarboxylic acid methyl ester)(9.30 g; 24.00 mmol) and solid $ZnCl_2$ (13.20 g; 97.00 mmol) in 200 mL toluene was heated to reflux for 48 hrs. The mixture was cooled, concentrated *in vacuo*, and the oil purified by chromatography (5% EtOAc in hexanes) to afford 0.50 g (1.35 mmol; 5.6%) of cyclized product which was taken on to the next step without further purification.

A solution of the above cyclized product (0.75 g; 2.03 mmol) and TEA (1.0 mL) in EtOH (40 mL) was treated with 10% Pd-C (100 mg) which had been pre-wetted with EtOH. The mixture was hydrogenated at atmospheric pressure for 16 hrs. The catalyst was filtered and the mother liquor concentrated *in vacuo*. The oil was purified by radial chromatography (10% then 15% EtOAc in hexanes) to afford 0.34 g (1.00 mmol; 50%) of 4-Benzyl-8-methoxy-1,2,3,4-tetrahydro-cyclopenta[b]indole-1-carboxylic acid methyl ester, compound 4, Scheme 1, as an oil. ^{1}H NMR ($CDCl_3$) δ 7.29-7.18 (m, 3H), 7.07 (d, J=8.7 Hz, 2H), 6.98 (app t, J=8.7 Hz, 1H), 6.80 (d, J=8.3 Hz, 1H), 6.47 (d, J=7.8 Hz, 1H), 5.19 (d, J=7.4 Hz, 2H), 4.20-4.14 (m, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 2.96-2.60 (m, 4H); IR ($CHCl_3$) 3008, 1729, 1563, 1496, 1449, 1435, 1259, 1172, 1109 cm^{-1}; HRMS calcd for $C_{21}H_{21}NO_3$: 335.1521. Found: 335.1526.

Part D.

A slurry of NH_4Cl (174 mg; 3.25 mmol) in toluene (7 mL)

at about 0 °C was slowly treated with trimethylaluminum (2N in toluene: 1.60 mL; 3.20 mmol). The cold bath was removed and the mixture stirred for 1 hr at ambient temperature (gas evolution ceased). A solution of 4-Benzyl-8-methoxy-1,2,3,4-tetrahydro-cyclopenta[b]indole-1-carboxylic acid methyl ester, (310 mg; 0.92 mmol) in 6 mL toluene:CH_2Cl_2 (5:1) was added dropwise and the reaction heated to 50 °C for 18 hrs. The mixture was allowed to cool, quenched with 0.1 N aqueous HCl (10 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were washed with H_2O (50 mL) and concentrated in vacuo to afford a solid. Purification by radial chromatography (30% EtOAc in hexanes) afforded 158 mg (54%) of 4-Benzyl-8-methoxy-1,2,3,4-tetrahydro-cyclopenta[b]indole-1-carboxylic acid amide (compound 5, Scheme 1) as a white solid. ^1H NMR ($CDCl_3$) δ 7.28-7.21 (m, 3H), 7.09-7.00 (m, 4H), 6.87 (d, J=8.3 Hz, 1H), 6.55 (d, J=7.8 Hz, 1H), 5.19 (s, 2H), 4.12-4.07 (m, 1H), 3.95 (s, 3H), 3.12-3.04 (m, 1H), 2.99-2.92 (m, 1H), 2.73-2.61 (m, 2H); IR ($CHCl_3$) 3403, 3163, 1676, 1496, 1447, 1433, 1352, 1255, 1099, 775, 736, 699 cm^{-1}; HRMS calcd for $C_{20}H_{21}N_2O_2$: 321.1603. Found: 321.1607.

Part E.

A -20 °C slurry of 4-Benzyl-8-methoxy-1,2,3,4-tetrahydro-cyclopenta[b]indole-1-carboxylic acid amide (150 mg; 0.47 mmol) in CH_2Cl_2 (5 mL) was treated with BBr_3 (1 M in CH_2Cl_2: 4.70 mL; 4.70 mmol). The cold bath was removed and the reaction was stirred at ambient temperature for about 3 hours. The reaction was poured onto ice and the mixture extracted with CH_2Cl_2 (4x10 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a foam.

Purification by radial chromatography (40% EtOAc in hexanes) afforded 81 mg (0.26 mmol; 56%) 4-Benzyl-8-hydroxy-1,2,3,4-tetrahydro-cyclopenta[b]indole-1-carboxylic acid amide, compound 6, Scheme 1. ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 7.60 (br s, 1H), 7.34 (br s, 1H), 7.30-7.18 (m, 3H), 7.10 (d, J=7.3 Hz, 2H), 6.82-6.76 (m, 2H), 6.32 (dd, J=5.4 and 3.0 Hz, 1H), 5.20 (s, 2H), 3.99 (t, J=5.8 Hz, 1H), 2.87-2.79 (m, 1H), 2.73-2.60 (m, 3H); IR (KBr) 3347, 3190, 1656, 1594, 1562, 1496, 1452, 1352, 1250, 730 cm^{-1}; HRMS calcd for $C_{19}H_{19}N_2O_2$: 307.1447. Found: 307.1449.

Part F.

A solution 4-Benzyl-8-hydroxy-1,2,3,4-tetrahydro-cyclopenta[b]indole-1-carboxylic acid amide (75 mg; 0.24 mmol) in DMF (3 mL) at about 0 °C was treated with Triton-B (40% w/v in MeOH: 0.13 mL; 0.31 mmol) and the mixture stirred for 15 min. Methyl bromoacetate (0.07 mL; 0.74 mmol) was added dropwise. The reaction stirred at 0 °C for 1 hr, poured into 1 N aqueous HCl (10 mL), and the mixture diluted with EtOAc (10 mL). The two layers were separated and the aqueous phase extracted with EtOAc (4x40 mL). The combined organic layers were washed with 1 N aqueous HCl (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 103 mg of a solid. Purification by radial chromatography (10% then 15% then 25% then 40% EtOAc in hexanes) afforded 51 mg (56%) of (4-Benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid methyl ester compound 7, Scheme 1, as a white solid.

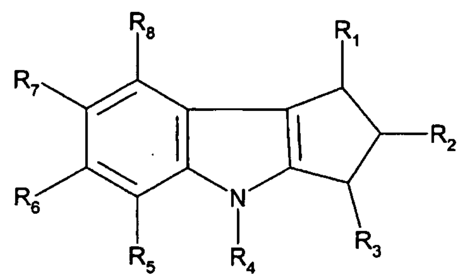
^1H NMR ($CDCl_3$) δ 7.36 (br s, 1H), 7.23-7.14 (m, 4H), 6.99 (d, J=8.6 Hz, 2H), 6.90 (app t, J=7.9 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 6.35 (d, J=7.3 Hz, 1H), 5.12 (s, 2H), 4.68 (AB q; J=15.6 and 50.1 Hz, 2H), 4.11-4.05 (m, 1H), 3.77 (s, 3H), 3.04-2.97 (m, 2H), 2.62-2.54 (m, 2H); IR (KBr) 3409, 1752, 1677, 1438, 1239, 1225, 1117, 734 cm^{-1}; FDMS, 379 (M+1); Anal calcd for $C_{22}H_{22}N_2O_4$.1.0 H_2O: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.80; H,5.80; N, 6.93.

Part G

A slurry of (4-Benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid methyl ester (24 mg; 0.06 mmol) in THF (2 mL) and MeOH (0.7 mL) was treated with 1N aqueous LiOH (0.1 mL). The mixture was stirred for 14 hrs and was concentrated in vacuo. Purification by reverse phase chromatography (Vydac C_{18} column; 5% to 70% of 0.1% HCl/H_2O in 0.1% HCl/CH_3CN) afforded 21 mg (92%) (4-Benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, compound 8, Scheme 1, as a white solid. ^1H NMR ($CDCl_3$) δ 7.30-7.19 (m, 4H), 7.09 (d, J=7.3 Hz, 2H), 6.98 (d, J=8.8 Hz, 1H), 6.87 (app t, J=7.8 Hz, 1H), 6.67 (br s, 1H), 6.42 (d, J=7.8 Hz, 1H), 5.25 (s, 2H), 4.66-4.51 (m, 2H), 3.85 (d, 7.8 Hz, 1H), 2.96-2.84 (m, 1H), 2.76-2.62 (m, 3H); IR (KBr) 3413, 1716, 1667, 1636, 1614, 1496, 1432, 1256, 1115, 721, 701 cm^{-1}; FDMS, 365 (M+1); Anal calcd for $C_{21}H_{20}N_2O_4$.0.5 HCl: C, 64.92; H, 5.40; N, 7.32. Found: C, 64.75; H,5.65; N, 7.13.

WE CLAIM:

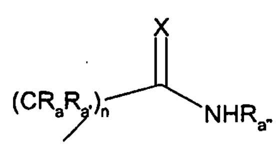
1. A tricyclic compound represented by the formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof;



(I)

wherein;

R_1 is an amide, thioamide or hydrazone group represented by the formulae,



wherein X is oxygen or sulfur; R_a and $R_{a'}$ are independently selected from hydrogen, (C_1-C_8)alkyl, or aryl; $R_{a''}$ is hydrogen, NH_2, (C_1-C_8)alkyl, aryl, (C_1-C_8)alkylaryl, or arylalkyl; and n is 0, 1, or 2.

R_2, and R_3 are independently hydrogen, or a group containing 1 to 10 non-hydrogen atoms plus any required hydrogen atoms;

R_4 is the group (C_1-C_{20})alkyl, (C_1-C_{20})haloalkyl, (C_2-C_{20})alkenyl, (C_2-C_{20})alkynyl, (C_1-C_{10})alkylaryl, $(C_1-$

C_5)alkylcyclohexyl, (C_1-C_5)alkylcyclopentyl, (C_1-C_5)alkylcycloheptyl, phenyl, benzyl, methylnaphthyl, (C_1-C_5)alkylheterocyclic, carbocyclic radical, or heterocyclic radical, or aryl;

R_5, R_6, and R_7 are independently selected from hydrogen and non-interfering substituents;

R8 is the group, -(La)-(acidic group) wherein -(L_a)-, is an acid linker having an acid linker length of 1 to 8;

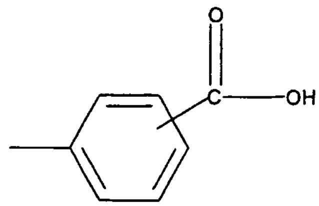
2. The compound of Claim 1 wherein R_3 is hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, -O-(C_1-C_3 alkyl), -S-(C_1-C_3 alkyl), (C_3-C_4)cycloalkyl, -CF_3, halo, -NO_2, -CN, or -SO_3.

3. The compound of claim 1 wherein R_8 is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

-COOH

-5-tetrazolyl,

-SO3H,



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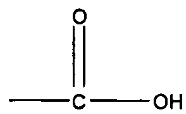
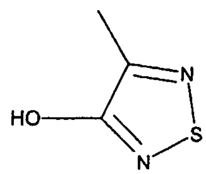
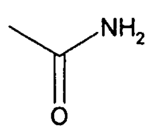


or

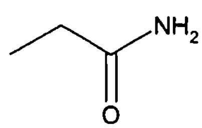


4. The compound of Claim 1 wherein R_1 is the group represented by the formula;



,

5. The compound of Claim 1 wherein R_1 is the group



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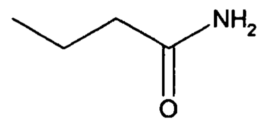
6. The compound of Claim 1 wherein R_1 is the group



7. The compound of Claim 1 wherein, for R_5 or R6 or R_7, the non-interfering substituent is independently selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8) alkynyl, (C_7-C_{12})arylalkyl, (C_7-C_{12})alkylaryl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkenyl, phenyl, toluyl, xylenyl, benzyl, biphenyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyloxy, (C_2-C_8)alkynyloxy, (C_2-C_{12})alkoxyalkyl, (C_2-C_{12})alkoxyalkyloxy, (C_2-C_{12})alkylcarbonyl, (C_2-C_{12})alkylcarbonylamino, (C_2-C_{12})alkoxyamino, (C_2-C_{12})alkoxyaminocarbonyl, (C_1-C_{12})alkylamino, (C_1-C_6)alkylthio, (C_2-C_{12})alkylthiocarbonyl, (C_1-C_8)alkylsulfinyl, (C_1-C_8)alkylsulfonyl, (C_2-C_8)haloalkoxy, (C_1-C_8)haloalkylsulfonyl, (C_2-C_8)haloalkyl, $C_1-C_8)$hydroxyalkyl, $-C(O)O(C_1-C_8$ alkyl), $-(CH_2)_n-O-(C_1-C_8)$alkyl), benzyloxy, phenoxy, phenylthio, $-(CONHSO_2R)$, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8, and R is (C_1-C_4)alkyl, phenyl or (C_7-C_{12})aryl.

8. The compound of claim 1 wherein R_8 is the group, $-(L_a)-$(acidic group) and wherein the (acidic group) is selected from the group consisting of -COOH, -COONa, and -COOK.

9. The Compound of Claim 1 wherein the prodrug is the methyl or ethyl or N-methylmorpholino ester of a compound of formula (I).

10. A compound selected from the group consisting of:

(4-benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(4-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(4-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cyclopropylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cyclobutylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cyclopentylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(cycloheptylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(3-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(4-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(1-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,3-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,

(4-[(3,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,3-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(2,6-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-[(3,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid,
(4-benzyl-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-phenoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-fluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(4-chlorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(2-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-bromophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-iodophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-acetamidophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-carbamoylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(3-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-methylsulfonylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-methylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-ethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-trifluoromethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cyclopropylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cyclobutylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(cyclopentylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

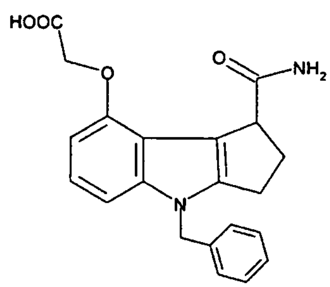
(4-[(cycloheptylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-methoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-ethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-trifluoromethoxyphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-cyanophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-pyridyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

(4-[(2-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-furyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-thienyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-benzyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(4-phenylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(1-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2-napthyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,3-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,

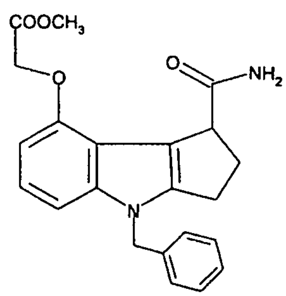
(4-[(3,4-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,5-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,6-difluorophenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
2,3-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(2,6-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,4-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(3,5-dimethylphenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, methyl ester,
(4-[(phenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, morpholinoethyl ester,
(4-[(cyclohexyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, morpholinoethyl ester,
(4-[(cyclopentyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-8-yloxy)-acetic acid, morpholinoethyl ester,

(4-[(phenyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydrocyclopenta[b]indol-8-yloxy)-acetic acid, N,N-diethylacetamido ester,
(4-[(cyclohexyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydrocyclopenta[b]indol-8-yloxy)-acetic acid, N,N-diethylacetamido ester, and
(4-[(cyclopentyl)methyl]-1-carbamoyl-1,2,3,4-tetrahydrocyclopenta[b]indol-8-yloxy)-acetic acid, N,N-diethylacetamido ester.

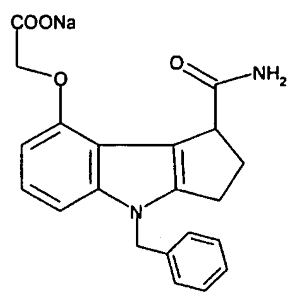
11. A tricyclic compound represented by the formulae (C1), (C2), or (C3):



C1



C2



C3

12. A pharmaceutical formulation comprising a tricyclic compound of formula (I) together with a pharmaceutically acceptable carrier or diluent.

13. A method of inhibiting $sPLA_2$ mediated release of fatty acid comprising contacting $sPLA_2$ with a therapeutically effective amount of tricyclic compound of formula (I).

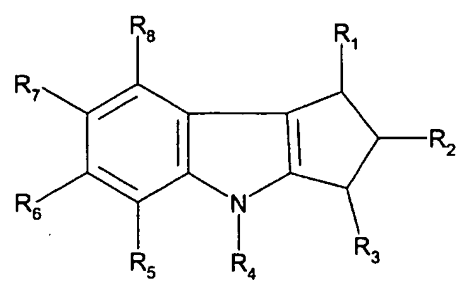
14. A method of treating a mammal, including a human, to alleviate the pathological effects of Inflammatory Diseases; wherein the method comprises administering to said mammal a therapeutically effective amount of a tricyclic compound of formula (I).

15. A pharmaceutical formulation containing a therapeutically effective amount of the compound of formula (I) useful for the treatment and/or amelioration of Inflammatory Diseases.

16. A pharmaceutical formulation containing a therapeutically effective amount of the compound of formula (I) useful for inhibiting $sPLA_2$ mediated release of fatty acid.

17. Use of a pharmaceutical composition comprising a therapeutically effective amount of $sPLA_2$ inhibitor compounds according to formula (I) and mixtures thereof for the manufacture of a medicament for the treatment of Inflammatory Diseases.

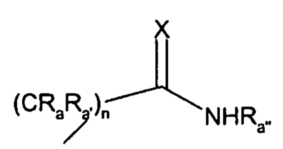
18. Use of a compound of formula I for the manufacture of a medicament for the treatment and/or prevention of Inflammatory Diseases comprising administering a therapeutically effective amount of a tricyclic compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(I)

wherein;

R_1 is an amide, thioamide or hydrazone group represented by the formulae,



wherein X is oxygen or sulfur; R_a and $R_{a'}$ are independently selected from hydrogen, (C_1-C_8)alkyl, or

aryl; $R_{a''}$ is hydrogen, NH_2, (C_1-C_8)alkyl, aryl, (C_1-C_8)alkylaryl, or arylalkyl; and n is 0, 1, or 2.

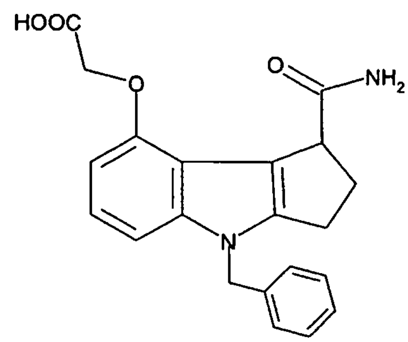
R_2, and R_3 are independently hydrogen, or a group containing 1 to 10 non-hydrogen atoms plus any required hydrogen atoms;

R_4 is the group (C_1-C_{20})alkyl, (C_1-C_{20})haloalkyl, (C_2-C_{20})alkenyl, (C_2-C_{20})alkynyl, (C_1-C_{10})alkylaryl, (C_1-C_5)alkylcyclohexyl, (C_1-C_5)alkylcyclopentyl, (C_1-C_5)alkylcycloheptyl, phenyl, benzyl, methylnaphthyl, (C_1-C_5)alkylheterocyclic, carbocyclic radical, or heterocyclic radical, or aryl;

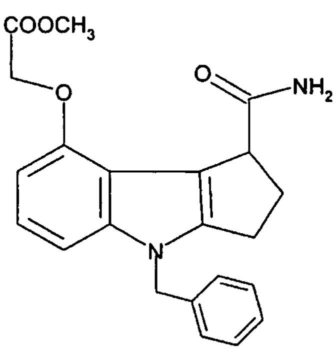
R_5, R_6, and R_7 are independently selected from hydrogen and non-interfering substituents;

R8 is the group, -(La)-(acidic group) wherein $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

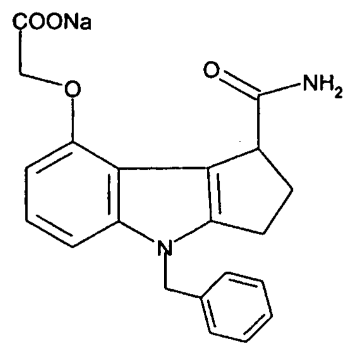
19. Use of a compound of formula I for the manufacture of a medicament for the treatment or prevention of Inflammatory Diseases comprising administering a therapeutically effective amount of a tricyclic compound represented by the formulae (C1), (C2), or (C3):



C1



C2



C3

INTERNATIONAL SEARCH REPORT

I onal Application No
PCT/US 02/21298

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/94 A61K31/404 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 950 661 A (LILLY CO ELI) 20 October 1999 (1999-10-20) claim 1 ---	1-19
Y	WO 00 07591 A (MIHELICH EDWARD DAVID ;WARSHAWSKY ALAN M (US); LILLY CO ELI (US);) 17 February 2000 (2000-02-17) claim 1 ---	1-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

14/10/2002

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Lauro, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/21298

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D. J. DAVIES: "Mapping the melatonin receptor. 5. Melatonin agonists and antagonists derived from tetrahydrocyclopent'b!indoles, tetrahydrocarbazoles and hexahydrocyclohept'b!indoles" J. MED. CHEM., vol. 41, no. 4, 1998, pages 451-467, XP002215114 * see page 453, compounds (6); page 455 * -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/21298

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			BR	9901275	A	02-05-2000
			CN	1235968	A	24-11-1999
			CZ	9901371	A3	17-11-1999
			EP	1156050	A2	21-11-2001
			EP	0950661	A1	20-10-1999
			HU	9901219	A1	28-08-2000
			JP	11322745	A	24-11-1999
			NO	991823	A	18-10-1999
			NZ	335252	A	24-11-2000
			PL	332564	A1	25-10-1999
			TR	9900842	A2	21-09-2000
WO 0007591	A	17-02-2000	AU	5331499	A	28-02-2000
			EP	1100493	A1	23-05-2001
			JP	2002522386	T	23-07-2002
			WO	0007591	A1	17-02-2000